Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

18 May 2023

RSVPreF vaccine safety concerns.

The effect of breast feeding, known to reduce severity of RSV in babies, is not analysed. Dr Simões, lead author of the Phase 2 study, has written "The role of breast-feeding in preventing RSV disease and hospitalization for RSV is undisputed."

Might the fact that volunteers in USA who completed the study were reimbursed up to $1000, plus $100 for each unscheduled visit for RTI, affect their behavior in these trials?

Pfizer Phase 2 Trial

Preterm births: as reported in NEJM showed an excess of preterm births (Table S8) – 14/325 vs 1/78. OR= 3.47 (0.4489 to 26.7663)

Jaundice Neonatal (table S8) 11/325 vs 0/78 OR 8.42 (0.4902 to 144.5374).

Serious Jaundice (table S9) 8/325 vs 0/78 OR 4.20 (0.2400 to 73.6065).

In correspondence, the authors pointed out the lower-than-expected incidence of jaundice, which suggests that recording of adverse events was not properly done.

Pfizer Phase 3 Trial

What is the risk (see protocol para 5.2.1.6) that prior pregnancy complications at the time of consent, including prior preterm delivery ≤34 weeks' gestation and prior stillbirth or neonatal death, will "increase the risk associated with the participation in and completion of the study"?

"Early Premature births ≤ 34 weeks" (Table 1). 21/3568 vs 12/3558 OR 1.75 (0.8594 to 3.5613).

"Severe or life-threatening adverse events" of "Jaundice neonatal" (Table S17) 21/3568 vs 11/3558 OR 1.91 (0.9191 to 3.9654).

Statistically Significant adverse events (Phase 3)

Table S17 shows "severe or life-threatening adverse events" within 1 month of vaccination.

In the system class "Pregnancy, puerperium, and perinatal conditions" there is a statistically significant imbalance: 63/3682 vs 36/3675 OR 1.76 (1.1654 to 2.6570) **P = 0.0072**; particularly in the incidence of pre-eclampsia 17/3682 vs 7/3675 OR=2.43 (1.0067 to 5.868) **P = 0.0483**.

Long term studies are needed to confirm that there is no harm in delaying childhood RSV infection. See:

https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(22)00371-6/fulltext

"The study indicates that when the time for the first RSV infection is postponed or children are not recently reinfected, an increased number of older infants and children will be at risk of severe complications leading to hospital admission and mechanical ventilation. In infants younger than 3 months and children with comorbidities, the complications leading to intubation were mainly respiratory failure due to bronchiolitis, while children without risk factors for severe RSV disease had a wide range of atypical complications, including salbutamol-responsive wheeze, pneumothorax, bacterial pneumonia, cardiac failure, and CNS complications. These rare complications are important to be aware of, since new promising RSV-preventive interventions for healthy infants are currently being investigated. If such interventions postpone time to primary RSV infection, in the future, more older children might be admitted to hospital due to atypical complications, other than classic bronchiolitis."

Two instances of Guillain Barré-like syndrome were reported in Pfizer's RSV vaccine phase 3 trial in adults aged over 60.

If this vaccine is approved, what will be the recommendation for women with a previous preterm birth <34 weeks, or a previous stillbirth or neonatal death? These women were excluded from both trials.

Summary

Pfizer's results show a suggestion of an excess of preeclampsia, preterm births and neonatal jaundice, including those classed as "severe or life-threatening adverse events". This is concerning considering the GSK trial of a similar product being terminated when an excess of preterm babies and neonatal deaths was noticed. Babies born preterm are known to be more susceptible to RSV disease.

It is possible that the harms of these adverse events will be greater than any advantage in reducing medically attended RSV infections.

Hospitalization of the infant due to RSV infection in the first 12 months of life was a secondary endpoint of the Phase 3 study. There were 57 hospitalizations in the placebo group and 38 in the vaccinated group (Table S7).

These numbers (with similar denominators) seem to match the excess of "severe or life-threatening adverse events" within 1 month of vaccination in the mothers in the system class "Pregnancy, puerperium, and perinatal conditions", where 36 occurred in the placebo group and 63 in the vaccinated group, suggesting that any benefits to the infants were offset by serious harms to the mothers.